

Serial No. : 09/590,447
Filed : June 9, 2000

wherein R_2 is H or lower alkyl, R_4 is lower alkyl of 1 to 8 carbons and B is CH_2OH or $COOR_8$ where R_8 is H or ethyl.

REMARKS

Rejection Pursuant to 35 USC §112(2)

Claims 1-13 and 31-40 have been rejected under 35 USC §112(2) as being allegedly indefinite for use of the term "providing". The Examiner has indicated that the term "administering to a mammal in need thereof" would be favorably considered. Applicants thank the Examiner for this suggestion and have amended claims 1, 30 and 37 in light thereof.

The Applicants also thank the Examiner for indicating that the claims have been examined with regard to all species of organosilyl compounds of formula (3) and all disorders.

Prior Art

Applicants also thank the Examiner for indicating that the pending claims appear be free of the prior art. Thus, following the amendments made herein, the claimed method employing the organosilyl compounds of Formula (3) appears to be in condition for allowance.

The Examiner has asked that the pending claims be amended to eliminate compounds (1), (2) and (4) from claim 1 and 31. Applicants have done so herein, without prejudice to their later prosecution.

Respectfully submitted,

Dated: 10/14/02

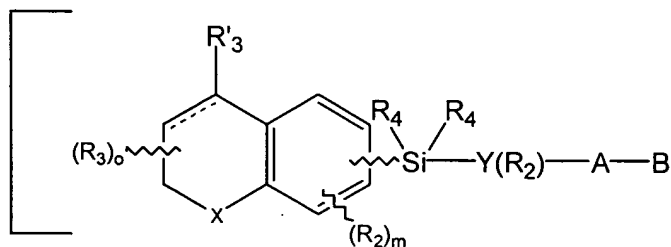
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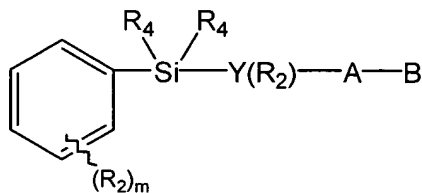
Serial No. : 09/590,447
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MARKED-UP VERSION OF THE AMENDED CLAIMS

1. (Amended) A method of treating a pathological condition in a mammal comprising the step of [providing] administering to a mammal in need thereof [to said mammal] a pharmaceutically acceptable composition comprising a synthetic FXR ligand able to stimulate, block, or inhibit the activity of a mammalian FXR receptor, said



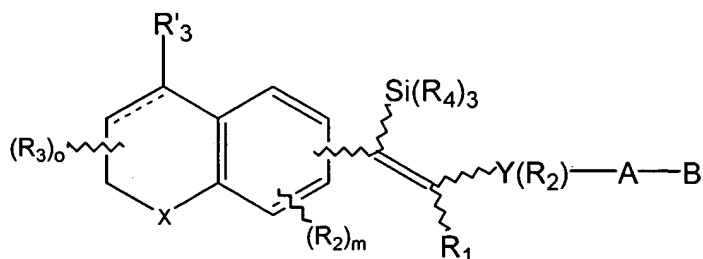
formula (1)



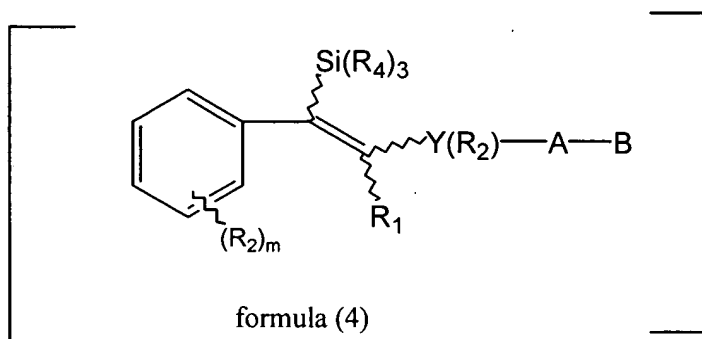
formula (2)

synthetic FXR ligand comprising a compound of the formula [selected from the group consisting of Formulas 1, 2, 3 and 4]

Serial No. : 09/590,447
 Filed : June 9, 2000



formula (3)



formula (4)

wherein the dashed line represents a bond or absence of a bond;

X is S, O, NR' where R' is H or alkyl of 1 to 6 carbons, or

X is $(C(R_1)_2)_n$ where R_1 is H or alkyl of 1 to 6 carbons, and n is an integer having the value of 0 or 1;

R_2 is hydrogen, lower alkyl of 1 to 6 carbons, F, Cl, Br, I, CF_3 , fluoro substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 12 carbons, or alkylthio of 1 to 12 carbons, benzyloxy or $C_1 - C_{12}$ alkylbenzyloxy;

R_3 is hydrogen, lower alkyl of 1 to 6 carbons or F;

m is an integer having the value of 0 - 3 [in Formulas (1) and (3) and 0 - 5 in Formulas (2) and (4)];

o is an integer having the value of 0 - 4 when the dashed line represents absence of a bond, and 0 - 3 when the dashed line represents a bond;

R_3 is hydrogen, lower alkyl of 1 to 6 carbons, F or $(R_{15})_r$ -phenyl, $(R_{15})_r$ -naphthyl,

Serial No. : 09/590,447
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or $(R_{15})_r$ -heteroaryl where the heteroaryl group has 1 to 3 heteroatoms selected from the group consisting of O, S and N, r is an integer having the values of 0 - 5;

R_4 is alkyl of 1 to 8 carbons, or phenyl;

Y is a phenyl or naphthyl group, or heteroaryl selected from a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and heteroaryl groups being optionally substituted with one or two R_2 groups;

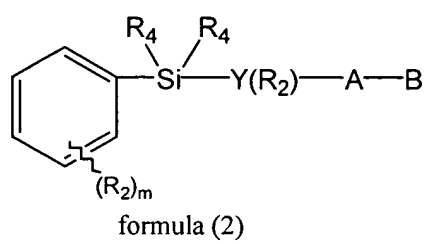
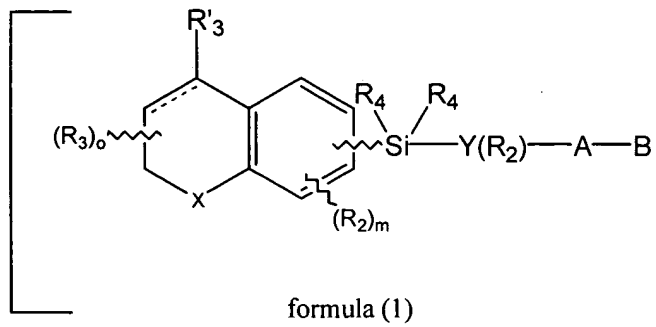
R_{15} is independently H, F, Cl, Br, I, NO_2 , $N(R_8)_2$, $NH(R_8)$, COR_8 , $NR_8CON(R_8)_2$, OH, $OCOR_8$, OR_8 , CN, an alkyl group having 1 to 10 carbons, fluoro substituted alkyl group having 1 to 10 carbons, an alkenyl group having 1 to 10 carbons and 1 to 3 double bonds, alkynyl group having 1 to 10 carbons and 1 to 3 triple bonds, or a trialkylsilyl or trialkylsilyloxy group where the alkyl groups independently have 1 to 6 carbons;

A is $(CH_2)_q$ where q is 0-5, lower branched chain alkyl having 3-6 carbons, cycloalkyl having 3-6 carbons, alkenyl having 2-6 carbons and 1 or 2 double bonds, alkynyl having 2-6 carbons and 1 or 2 triple bonds;

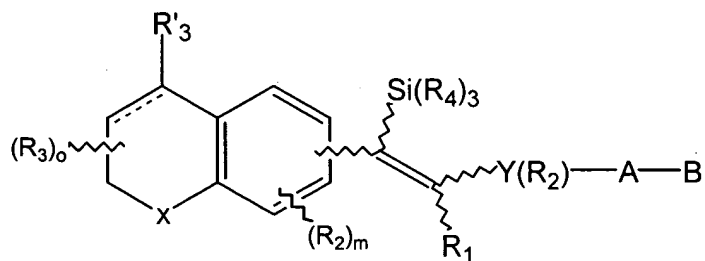
B is hydrogen, COOH, NO_2 , $P(O)(OH)_2$, $P(O)(OH)OR_8$, $P(O)(OR_8)_2$, SO_2OH , $SO_2(OR_8)$, $COOR_8$, $CONR_9R_{10}$, $-CH_2OH$, CH_2OR_{11} , CH_2OCOR_{11} , CHO, $CH(OR_{12})_2$, $CHOR_{13}O$, $-COR_7$, $CR_7(OR_{12})_2$, $CR_7OR_{13}O$, or tri-lower alkylsilyl, where R_7 is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R_8 is an alkyl group of 1 to 10 carbons or trimethylsilylalkyl where the alkyl group has 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or R_8 is phenyl or lower alkylphenyl, R_9 and R_{10} independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl, R_{11} is lower alkyl, phenyl or lower alkylphenyl, R_{12} is lower alkyl, and R_{13} is divalent alkyl radical of 2-5 carbons, or a pharmaceutically acceptable salt of said compound.

31. (Amended) A method of treating a hypercholesterolemic mammal comprising the steps: [providing] administering to a mammal in need thereof [said mammal with] a pharmaceutically acceptable composition comprising an FXR antagonist having the following formula [selected from Formulas 1, 2, 3, and 4]

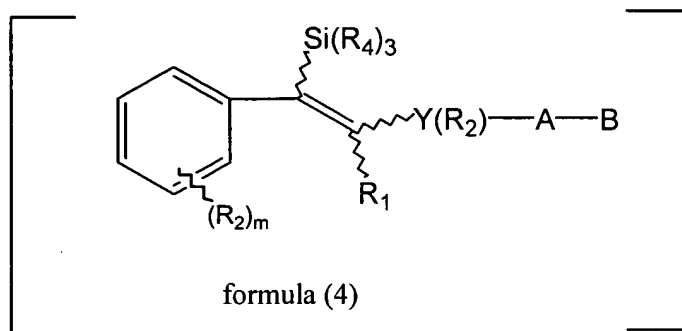
Serial No. : 09/590,447
 Filed : June 9, 2000



Serial No. : 09/590,447
 Filed : June 9, 2000



formula (3)



formula (4)

wherein the dashed line represents a bond or absence of a bond;

X is S , O , NR' where R' is H or alkyl of 1 to 6 carbons, or

X is $(C(R_1)_2)_n$ where R_1 is H or alkyl of 1 to 6 carbons, and n is an integer having the value of 0 or 1;

R_2 is hydrogen, lower alkyl of 1 to 6 carbons, F , Cl , Br , I , CF_3 , fluoro substituted alkyl of 1 to 6 carbons, OH , SH , alkoxy of 1 to 12 carbons, or alkylthio of 1 to 12 carbons, benzyloxy or $C_1 - C_{12}$ alkylbenzyloxy;

R_3 is hydrogen, lower alkyl of 1 to 6 carbons or F ;

m is an integer having the value of 0 - 3 [Formulas (1) and (3), and 0 - 5 Formulas (2) and (4)];

o is an integer having the value of 0 - 4 when the dashed line represents absence of a bond, and 0 - 3 when the dashed line represents a bond;

Serial No. : 09/590,447
Filed : June 9, 2000

R'_3 is hydrogen, lower alkyl of 1 to 6 carbons, F or $(R_{15})_r$ -phenyl, $(R_{15})_r$ -naphthyl, or $(R_{15})_r$ -heteroaryl where the heteroaryl group has 1 to 3 heteroatoms selected from the group consisting of O, S and N, r is an integer having the values of 0 - 5;

R_4 is alkyl of 1 to 8 carbons, or phenyl;

Y is a phenyl or naphthyl group, or heteroaryl selected from a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and heteroaryl groups being optionally substituted with one or two R_2 groups;

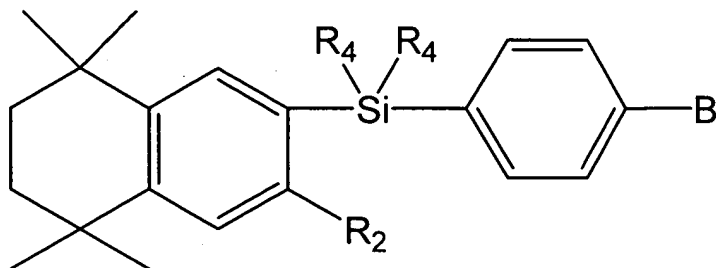
R_{15} is independently H, F, Cl, Br, I, NO_2 , $N(R_8)_2$, $NH(R_8)$, COR_8 , $NR_8CON(R_8)_2$, OH, $OCOR_8$, OR_8 , CN, an alkyl group having 1 to 10 carbons, fluoro substituted alkyl group having 1 to 10 carbons, an alkenyl group having 1 to 10 carbons and 1 to 3 double bonds, alkynyl group having 1 to 10 carbons and 1 to 3 triple bonds, or a trialkylsilyl or trialkylsilyloxy group where the alkyl groups independently have 1 to 6 carbons;

A is $(CH_2)_q$ where q is 0-5, lower branched chain alkyl having 3-6 carbons, cycloalkyl having 3-6 carbons, alkenyl having 2-6 carbons and 1 or 2 double bonds, alkynyl having 2-6 carbons and 1 or 2 triple bonds;

B is hydrogen, COOH, NO_2 , $P(O)(OH)_2$, $P(O)(OH)OR_8$, $P(O)(OR_8)_2$, SO_2OH , $SO_2(OR_8)$, $COOR_8$, $CONR_9R_{10}$, $-CH_2OH$, CH_2OR_{11} , CH_2OCOR_{11} , CHO, $CH(OR_{12})_2$, $CHOR_{13}O$, $-COR_7$, $CR_7(OR_{12})_2$, $CR_7OR_{13}O$, or tri-lower alkylsilyl, where R_7 is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R_8 is an alkyl group of 1 to 10 carbons or trimethylsilylalkyl where the alkyl group has 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or R_8 is phenyl or lower alkylphenyl, R_9 and R_{10} independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl, R_{11} is lower alkyl, phenyl or lower alkylphenyl, R_{12} is lower alkyl, and R_{13} is divalent alkyl radical of 2-5 carbons, or a pharmaceutically acceptable salt of said compound.

37. (Amended) A method of treating a pathological condition in a mammal comprising the step of [providing] administering to a mammal in need thereof [to said mammal] a pharmaceutically acceptable composition comprising a synthetic FXR ligand able to stimulate, block, or inhibit the activity of a mammalian FXR receptor, said synthetic FXR ligand having the formula

Serial No. : 09/590,447
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wherein R_2 is H or lower alkyl, R_4 is lower alkyl of 1 to 8 carbons and B is CH_2OH or $COOR_8$
where R_8 is H or ethyl.